J Rheumatol. 1995 Dec;22(12):2250-8.

Major role for interleukin 1 but not for tumor necrosis factor in early cartilage damage in immune complex arthritis in mice.

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OBJECTIVE: To determine the regulating role of interleukin-1 alpha and beta (IL-1 alpha, beta) and tumor necrosis factor alpha (TNF-alpha) on inhibition of proteoglycan synthesis and proteoglycan degradation in early immune complex arthritis (ICA) in the mouse. METHODS: In the early phases of arthritis, IL-1 and TNF were measured using cytokine specific bioassays, the NOB.1 EL-4 and L929 assay, respectively. The impact of IL-1 in proteoglycan synthesis was studied by neutralizing the formed IL-1 during early arthritis either by giving anti-IL-1 specific antibodies intravenously or IL-1 receptor antagonist (IL-1ra) intraperitoneally by osmotic pumps. TNF-alpha was neutralized by giving monoclonal antibodies directed against murine TNF-alpha. Synthesis of proteoglycans was measured ex vivo by uptake of 35S-sulfate by patellae derived from inflamed and control, noninflamed knee joints. In vivo formation of 35S-sulfate labeled proteoglycans was studied by autoradiography. Degradation of proteoglycans was measured by labeling patellae in vivo with 35S-sulfate before arthritis induction. RESULTS: High levels of IL-1 are formed during the first phase of immune complex arthritis (ICA). Neutralization of either IL-1 alpha or beta with specific polyclonal antibodies resulted only in partial blocking, whereas a combination fully blocked inhibition of proteoglycan synthesis. Full blocking was also found after systemic treatment with high amounts of IL-1 receptor antagonist (1.2 mg/day during 3 days). Influx of cells was also significantly reduced both in the anti-IL-1 as well as in the IL-1ra treated groups. Whether infiltrating cells are involved in inhibition of proteoglycan synthesis was further investigated in neutropenic mice. Significantly higher levels of IL-1 were found in arthritic joints of neutropenic compared with control mice. Suppression of proteoglycan synthesis was similar in arthritic knee joints of normal and neutropenic mice. However, only minor proteoglycan degradation was found in the latter. TNF-alpha was undetectable in the bioassay in early ICA and neutralization of TNF-alpha did not change either swelling, cell influx, proteoglycan synthesis or proteoglycan degradation. CONCLUSION: Local production of IL-1 in ICA in knee joints seems directly responsible for inhibition of proteoglycan synthesis. A direct role of IL-1 in proteoglycan loss is unlikely, but indirectly IL-1 may be involved in proteoglycan breakdown by attracting inflammatory leukocytes and activating synovial cells. TNF-alpha seemed to have no effect on either cell influx, proteoglycan synthesis or proteoglycan degradation in this model.

PMID: 8835558 [PubMed - indexed for MEDLINE]